Accelerated Complications in Type 2 Diabetes Mellitus: The Need for Greater Awareness and Earlier Detection

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Persistent hyperglycaemia is the underlying pathogenic factor responsible for chronic diabetic complications in Type 1 and Type 2 diabetes mellitus. In Type 1 diabetes, diagnosis is made soon after the onset of hyperglycaemia and several years are required for the resultant complications to appear clinically. The onset of Type 2 diabetes is insidious and is usually recognized only 5–12 years after hyperglycaemia develops. During this period of undiagnosed diabetes, hyperglycaemia, in combination with lifestyle factors (physical inactivity, alcohol use, smoking), and other metabolic (dyslipidaemia, obesity, insulin resistance) and haemodynamic (hypertension) abnormalities frequently associated with Type 2 diabetes, promote the initiation and progression of micro- and macrovascular complications. Furthermore, when blood glucose levels are increased only slightly and no symptoms are apparent, the physician may be reluctant to diagnose Type 2 diabetes or start treatment. This delay in diagnosing the disease results in a high prevalence of chronic complications at the time of actual diagnosis. Indeed, when Type 2 diabetes is diagnosed, cardiovascular disease and neuropathy are found in approximately 10% of cases, and retinopathy and nephropathy in 15–20%. All healthcare providers should be aware of this phenomenon, which may be termed 'accelerated complications', and should plan thorough screening programmes for these conditions at diagnosis. All reversible risk factors associated with diabetes should be identified and treated. When acute metabolic derangements and infections are not the main causes of morbidity and mortality in diabetes, the costs of diabetes care are related mainly to chronic complications of the disease. Therefore, because of the high frequency of Type 2 diabetes, the most efficient method of reducing costs is to increase awareness and secure earlier detection that leads to fast and aggressive treatment of the accelerated chronic complications often seen in Type 2 diabetes.

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Introduction

Persistent hyperglycaemia is the underlying pathogenic mechanism responsible for chronic diabetic complications in Type 1 and Type 2 diabetes. In Type 1 diabetes, diagnosis is made soon after the onset of hyperglycaemia and several years are required for the resultant complications to appear clinically. The onset of Type 2 diabetes is insidious and is usually recognized only 5–12 years after hyperglycaemia develops.[1] This is generally a result of the long phase of mild hyperglycaemia in Type 2 diabetes, which is well tolerated by the patient and is often underestimated by the physician. Indeed, asymptomatic hyperglycaemia is sometimes considered only a biochemical abnormality with no substantial clinical implication. This leads to the conclusion that a thorough screening for chronic complications of diabetes is unnecessary. However, the two cases described here contradict this belief and provide evidence to support more appropriate medical practices.

Case 1

A 46-year-old man was admitted to hospital because of gangrene of the first and second toe of the left foot. The patient, a male nurse, had been diagnosed as having mild hyperglycaemia one year earlier when he consulted his family physician because of skin lesions with poor healing on the toes of the left foot. On that occasion the patient was prescribed gliclazide 80 mg twice daily. However, the patient showed poor compliance and over the next months he never consulted his doctor. The

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patient had a positive family history of Type 2 diabetes and reported low levels of physical activity and cigarette smoking (15–20 per day) for many years, but had no previous major health problems. On physical examination, bruits on both sides of the neck were heard; pedal pulses were not detected; leg muscles were slightly hypotrophic; leg deep-tendon reflexes were absent; sensation was reduced on testing with light touch, pinprick and vibration; body weight was 92 kg; height was 176 cm; blood pressure was 165/105 mmHg; and heart rate was 86 beats per minute. On admission, laboratory tests showed erythrocyte sedimentation rate (ESR) at 122 $mm \cdot h^{-1}$, fibrinogen 801 $mg \cdot dl^{-1}$ (normal range 150–450 $mg \cdot dl^{-1}$), haematocrit 47%, white cell count 10 800 per mm^3, neutrophils 78%, glucose 327 $mg \cdot dl^{-1}$ (18.2 $mmol \cdot l^{-1}$), HbA_{1c} 9.2%, cholesterol 242 $mg \cdot dl^{-1}$ (6.3 $mmol \cdot l^{-1}$), triglyceride 312 $mg \cdot dl^{-1}$ (3.5 $mmol \cdot l^{-1}$), high density lipoprotein (HDL) cholesterol 32 $mg \cdot dl^{-1}$ (0.83 $mmol \cdot l^{-1}$) and creatinine 1.4 $mg \cdot dl^{-1}$ (124 $\mu mol \cdot l^{-1}$). Urine was positive for protein (1.2 $g \cdot day^{-1}$) and glucose, and negative for ketones; the sediment contained three hyaline casts per low-power field and four red cells per high-power field. Other laboratory tests were normal. An electrocardiogram showed Q waves in II, III and aVF leads, which suggests a past (unrecalled) inferior myocardial infarction. A radiograph of the left foot showed partial amputation of the distal phalanx of the first toe and arterial wall calcifications. Arterial Doppler examination of the legs revealed diffuse sclerosis and arteriography showed occlusion of the left superficial femoral artery with partial revascularization of the popliteal artery by collateral vessels. Sonography of the carotid arteries revealed carotid plaques on both sides and a fundus examination showed diabetic background retinopathy.

Clinical Diagnosis

Type 2 diabetes, diffuse macroangiopathy with ischaemic gangrene of the first and second toe of the left foot, past myocardial infarction, nephropathy and background retinopathy.

Case 2

A 61-year-old woman was admitted to the hospital because of hyperglycaemia revealed by laboratory work-up for urinary symptoms (dysuria, urgency, frequent urination and suprapubic pain) and a mild increase in body temperature (37.5–38.0 °C). The patient had always been well but over the last few years she had periods of unexplained polyuria, nocturia and polydipsia. She reported blurred vision over the last few weeks. Family history of diabetes was negative. The patient had four babies between the age of 25 and 40, the last two with a birthweight of 4.3 and 4.8 kg. She reported low levels of physical activity and excess weight since the first pregnancy, and smoked 5–10 cigarettes per day between the age of 17 and 32. Body weight increased substantially during the last two pregnancies and after the menopause, but she never followed a diet regularly. On physical examination, body weight was 85 kg and height was 157 cm, blood pressure was 175/110 mmHg, heart rate was 102 beats per minute, and a bruit on the right side of the neck was heard. Laboratory tests showed ESR was 76 $mm \cdot h^{-1}$, fibrinogen 420 $mg \cdot dl^{-1}$, haematocrit 38%, white cell count 12 000 per mm^3, neutrophils 81%, glucose 264 $mg \cdot dl^{-1}$ (14.7 $mmol \cdot l^{-1}$), HbA_{1c} 10.2%, cholesterol 288 $mg \cdot dl^{-1}$ (7.4 $mmol \cdot l^{-1}$), triglyceride 286 $mg \cdot dl^{-1}$ (3.2 $mmol \cdot l^{-1}$), HDL cholesterol 36 $mg \cdot dl^{-1}$ (0.9 $mmol \cdot l^{-1}$) and creatinine 1.2 $mg \cdot dl^{-1}$ (106 $\mu mol \cdot l^{-1}$). Urine was positive for protein (++++) and glucose (++++), and negative for ketones; the sediment contained red blood cells, leucocytes and bacteria. Urine culture showed an infection by *Escherichia coli*. An electrocardiogram revealed left ventricular hypertrophy and radiographs of the chest showed enlargement of the left ventricle. Macular oedema in the right eye and bilateral non-proliferative retinopathy were detected by retinal examination. An echo-duplex of the carotid arteries revealed an 80% stenosis of the right internal carotid artery and several plaques in the common and internal carotid arteries on both sides.

Clinical Diagnosis

Type 2 diabetes, obesity, urinary tract infection, hypertension, hypertensive heart disease, carotid stenosis and retinopathy.

Comments

In the first case, ischaemic gangrene of toes led to the detection of diffuse macroangiopathy (coronary and carotid arteries) and microangiopathy (nephropathy, retinopathy and neuropathy). In the second case, the urinary tract infection revealed diabetes complicated already by retinopathy, carotid artery stenosis and hypertensive heart disease. These two cases are typical examples of a frequent clinical event in which the diagnosis of Type 2 diabetes is established only when an intercurrent disease troubles the patient. The presence of Type 2 diabetes could have been diagnosed long before the acute episode on the basis of clinical signs and symptoms, but no medical investigation was undertaken. The recognition of several associated metabolic disorders and chronic complications of diabetes was made at the same time as the diagnosis of the disease.

These examples point out that a long period of hyperglycaemia precedes the diagnosis of Type 2 diabetes because the elevation of blood glucose is moderate (140–200 $mg \cdot dl^{-1}$; 7.7–11.0 $mmol \cdot l^{-1}$) and does not result in signs and symptoms severe enough to draw the attention of the patient or the physician. Furthermore, when blood glucose is increased only slightly and no symptoms trouble the patient, the physician is sometimes

reluctant to make the diagnosis and begin treatment. In addition, even before blood glucose reaches levels diagnostic for diabetes, there is a long period characterized by mild fasting hyperglycaemia (110–140 $mg \cdot dl^{-1}$; 6.1–7.7 $mmol \cdot l^{-1}$) and large postprandial increments of blood glucose levels.

Mild to moderate hyperglycaemia during the period of 'pre-diabetes' (actual early stages of diabetes) is sufficient to promote the initiation and progression of chronic complications. Hyperglycaemia operates in concert with lifestyle factors (excessive calorie intake, low level of physical activity, cigarette smoking), and other metabolic (dyslipidaemia, obesity, insulin resistance) and haemodynamic (arterial hypertension) abnormalities, associated frequently with Type 2 diabetes. With respect to these factors, it is worth noting that approximately 70% of patients with newly diagnosed Type 2 diabetes are overweight and as many as 60% have dyslipidaemia or arterial hypertension.[1] These abnormalities often precede Type 2 diabetes diagnosis by several years, are frequently untreated and contribute to the development of atherosclerosis as well as microangiopathy. The diagnosis of diabetes is therefore preceded by a long period featured not only by hyperglycaemia but also by a cluster of associated risk factors that remain totally untreated. As a consequence, in patients with undiagnosed diabetes, a high prevalence of chronic complications occurs, e.g. angina pectoris (approximately 10%), myocardial infarction (approximately 6%), peripheral vascular disease (approximately 10%), carotid stenosis (approximately 10%), peripheral neuropathy (approximately 10%), nephropathy (approximately 20%) and retinopathy up to 30%.[1–4]

Interestingly, asymptomatic hyperglycaemia has been recently shown to be associated with increased mortality.[5] Furthermore, other prospective studies have reported that during follow up the overall mortality (60–70% from cardiovascular diseases) was even greater in patients with undiagnosed diabetes at baseline than in known diabetic individuals.[6,7] These data stress the importance to society and the healthcare system of the burden of undiagnosed Type 2 diabetes and its 'accelerated complications'. All healthcare providers should be aware of this phenomenon and should look for signs of diabetes whenever clinically suspected (signs, symptoms, risk factors), pay the appropriate attention to any abnormality (even borderline) of blood glucose levels and should plan a thorough screening of chronic complications from the time of diagnosis of diabetes. Meanwhile, all reversible risk factors associated with diabetes should be identified and treated. Indeed most recently, the United Kingdom Prospective Diabetes Study (UKPDS) has shown conclusively that intensive treatment of hyperglycaemia[8] and hypertension[9] is very effective in reducing the risk of adverse diabetes-related outcomes.

In times when acute metabolic derangements and infections are no longer the main causes of morbidity and mortality in diabetes, the costs society pays for diabetes care are mainly related to chronic complications of the disease. As a result of the large preponderance of Type 2 vs. Type 1 diabetes, the most efficient way to reduce these costs is to promote increased awareness, and implement early detection programmes and aggressive treatment of the accelerated chronic complications of Type 2 diabetes. The recent proposal from the American Diabetes Association to reduce the cut-off values for diabetes diagnosis could favour earlier detection and initiation of programmes to prevent the accelerated complications.[10]

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